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REVIEW ARTICLE

Corticosteroid Therapy in Management of Myocarditis Associated with COVID-19; a Systematic Review of Current Evidence

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Abstract: **Introduction:** Myocarditis in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seems to be associated with a higher mortality rate. This study aims to summarize the latest evidence on whether the use of corticosteroids in patients with myocarditis associated with COVID-19 is necessary. **Methods:** We performed an extensive search using a combination of search terms in PubMed, Europe PMC, ProQuest, EBSCOhost, and Google Scholar up to January 2021. Full-text articles that met the predefined inclusion criteria were included in the present study. **Results:** The full-texts of 18 articles have been reviewed. Thirteen out of the eighteen (72%) patients who got corticosteroid administration experienced major clinical improvements during follow-up while the other five (28%) were experiencing uneventful events. The mean age of the reported patients was 47.8±13.2 years. There was no gender predominance. Most of the reported cases were from USA (39%) followed by Spain, China, and UK (11% each), while Brazil, Colombia, France, Belgium, and Italy contributed one case each. Various corticosteroids were used but the most commonly applied were methylprednisolone (89%), hydrocortisone (5.5%), and prednisolone (5.5%). The most common route of administration among the studies was intravenous administration and the duration of treatment varied between one and fourteen days. **Conclusion:** A review of the currently available literature shows that with the use of corticosteroid agents in treating myocarditis associated with COVID-19, favorable outcomes are attainable. Well-established randomized clinical trials are needed to evaluate the efficacy and safety of using corticosteroids in this condition.

Keywords: COVID-19; myocarditis; corticosteroid; treatment

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1. Introduction

Late in 2019, the world was staggered by the emergence of a new virus derived from Wuhan, China, which caused severe pneumonia and was later called the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The diease caused by the virus was named coronavirus disease 19 (COVID-19) (1). This disease has led to more than 20 million active cases in 218 countries with more than 1.5 million people losing their lives (2). In the midst of this pandemic, a lot is still yet to be discovered, including the true magnitude of the disease. It was later discovered that since it binds with angiotensin converting enzyme (ACE) 2 receptors, which are also present in endothelial cells, it also affects the cardiovascular system and could manifest as myocarditis (3, 4). As many studies investigating the mechanism of multiple organ dysfunction syndrome (MODS) associated with COVID-19 indicated, systemic hyper inflammation syndrome has become a leading theory to explain the condition (5). Currently, there is no guideline that specifically addresses use of corticosteroids in treatment of myocarditis caused by COVID-19. Considering that uncertainty remains regarding this issue, we aimed to systematically review the use of corticosteroids in patients with myocarditis associated with COVID-19. We hypothesized that the addition of immunosuppressant therapy e.g. corticosteroids at this stage may reduce the severity of this hyperinflammatory condition.

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2. Methods

2.1. Protocol and Registration

This systematic review was conducted in line with the Cochrane Handbook for Systematic Reviews of Interventions and reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (6, 7). The protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO), under registration number CRD42020223524.

2.2. Search Strategy

Due to the lack of research articles, we performed a comprehensive search on case reports/series that presents patients with myocarditis associated with COVID-19 who were treated with corticosteroids using keywords ((COVID 19) OR (COVID-19) OR (Coronavirus) OR (Coronavirus disease) OR (Novel Coronavirus) OR (Novel human coronavirus) OR (SARS coronavirus) OR (SARS-CoV2) OR (SARS-CoV-2) OR (SARS CoV-2) OR (2019-nCoV)) AND ((Myocarditis) OR (Carditis) OR (Pericarditis) OR (Myopericarditis)) AND (Corticosteroid)) from the time in which SARS-CoV-2 was identified (January 2020) up until January 2021 through PubMed, EuropePMC, ProQuest, EBSCOhost, and Google Scholar. To ensure the identification of all relevant articles and publications, hand-searched articles from reference lists were also reviewed as an additional source of studies. We did not include words related to the outcomes of interest in order to obtain the largest number of search results possible. Our search was in line with PRISMA guidelines and the flowchart in Figure 1 portrays the search and screening processes.

2.3. Eligibility Criteria

In the present study, all cases using corticosteroids for patients with myocarditis associated with COVID-19 were included to be reviewed. Exclusion criteria comprised animal studies, expert opinions, literature review studies, news articles, letters, editorials, guidelines, and any studies that did not mention the outcomes and specify the corticosteroid used in the study. We also limited our search to articles written in English. The outcomes of interest were all-cause mortality, clinical improvement, and hospital discharge.

2.4. Study Selection and Data Collection Process

Articles were sorted based on whether titles or abstracts met the inclusion criteria. Full-text articles were then read, any duplicate studies were deleted, and those that did not satisfy the inclusion criteria were excluded. Data from the article were extracted and summarized using predesigned tables that consisted of name of the first author, year of publication, country in which the study was conducted, age and sex distribution of the patients, complete assessment of the patient, corticosteroid used, dose, route, and duration of administration, other medications, and outcomes. All steps of study selection and data collection process were conducted by all authors. Disagreements regarding study selection and data extraction were resolved through consensus-based discussion.

2.5. Risk of Bias Assessment

Two independent reviewers critically assessed the included studies using The Joanna Briggs Institute's critical assessment tool for case reports (8). The presence of bias was determined for each article using the checklist of eight questions included in Table 2. The articles received a score to indicate their degree of bias (low (included) and high (excluded)). For the purpose of this study, if "yes" was answered for more than half of the eight questions on the checklist, the study was considered to have a low risk of bias. Otherwise, answering "no" or “unclear” to half or more of the eight questions means the study was ascertained to have a high risk of bias and was excluded from this systematic review. Discrepancies in quality ratings were resolved through consensus-based discussion.

3. Results

3.1. Study Selection and Characteristics

Five databases were used to find articles related to the use of corticosteroid in myocarditis associated with COVID-19. We found 3479 articles; out of which, eighteen case reports were then deemed eligible for inclusion in the present study (9-26). A PRISMA flow diagram detailing the process of identification, screening, inclusion, and exclusion of studies is shown in Figure 1. The mean age of the reported patients was 47.8±13.2 years (range 18–69 years). There was no gender predominance. Most of the reported cases were from USA (39%) followed by Spain, China, and UK (11% each), while Brazil, Colombia, France, Belgium, and Italy contributed one case each. Various corticosteroids were used but the most commonly applied were methylprednisolone (89%), hydrocortisone (5.5%), and prednisolone (5.5%). The most common route of administration among the studies was intravenous administration and the duration of treatment varied between one and fourteen days. Other drugs were also used as combination therapy along with corticosteroids. Table 1 recounts the characteristics of the included studies.

3.2. Risk of Bias within Studies

All articles were determined to have low risk of bias. Seven other studies were identified as having high risk of bias and were excluded from the final inclusion process. Overall, studies did not report the adverse events resulting from the interventions. Moreover, low-level evidence from the included

studies could not explain the causal relationship between the interventions and the outcomes. A complete risk of bias assessment of the comprised studies is displayed in Table 2.

4. Discussion

Eighteen case reports administering corticosteroids to subjects with myocarditis associated with COVID-19 were included in this systematic review. These case reports described several types of corticosteroids, doses, routes of administration, and various outcomes. For instance, in the Colombian study conducted by Bernal-Torres et al. (9), the authors described a 38-year-old woman without any comorbid conditions presenting with palpitations as well as general malaise since 3 days prior to admission. The patient had positive PCR examination on nasal swab for COVID-19. Furthermore, the patient was diagnosed with fulminant myocarditis associated with COVID-19 and was treated with intravenous immunosuppressant in the form of methylprednisolone. As a result, the patient experienced clinical improvement and was discharged on day 16. Case reports with similar population, without comorbid conditions, and with similar steroid therapy regimen were also provided by Garau et al. (12), Hu et al. (13), and Naneishvili et al. (19). They showed progressive clinical improvements in various aspects. Higher dose of methylprednisolone was also found to provide good clinical improvements in studies performed by Salamanca et al. (22) and Sampaio et al. (23). Some patients with certain comorbidities such as hypertension (11, 18), heart failure (15), and type 1 diabetes mellitus (21) showed clinical improvements as well. In addition, there were also various studies that did not specify the steroid dose used (14, 16). Besides, it was not uncommon to use other types of corticosteroids such as hydrocortisone (11) as well as oral prednisolone (24), which provided good clinical improvements as well.

Each and every study used other therapeutic agents, such as antibiotics (67%), hydroxychloroquine (50%), immunoglobulin (38%), antiviral drugs (27%), immunomodulators (27%), colchicine (22%), and other agents in addition to corticosteroid therapy to manage myocarditis associated with COVID-19 in patients. Regarding the outcomes, at the time of submission of those case reports, the majority of patients had survived (72%). Most of the patients who reportedly passed away were noted to have both acute respiratory distress syndrome (ARDS) and multiple-organ failure (Table 1).

Most of the cases in this study were reported in sufficient detail; however, four reports did not specify the dose of the corticosteroid used and three of them did not report the duration of the corticosteroid's usage. The use of corticosteroids in myocarditis associated with COVID-19 seemed to have a better outcome in this small study. From the majority of those who got myocarditis from COVID-19 infection, good outcomes were reported more in those undergoing corticosteroid therapy (thirteen out of eighteen patients) compared with those who did not take a corticosteroid (five out of eighteen patients).

The plausible explanation for these is that according to current researches, higher concentration of proinflammatory cytokines and chemokines were detected in patients with multiple organ dysfunction syndrome associated with COVID-19 due to exaggerated immune response to the virus (27). Based on this mechanism, corticosteroids can be clinically utilized to prevent the immune system from attracting more inflammatory cells to the tissue e.g. cardiac, which reduces inflammation (28).

Recently, the European Society of Cardiology has issued a guidance in dealing with cardiovascular manifestations of COVID-19, yet there is no clear recommendation for the treatment of myocarditis associated with SARS-CoV-2 (29). Myocarditis is a potentially life-threatening disease. For this reason, from the current evidence that was drawn from this systematic review, the authors of this study proposed that corticosteroid must be considered as a last resort in terms of treating patients with myocarditis associated with COVID-19. This systematic review pooled case reports of patients with myocarditis caused by COVID-19 infection. Since this is a pooled case report, the evidence is weaker than controlled clinical trials. The number of cases was also small; there were only 18 cases from 18 studies. The findings of the pooled case reports might not apply to all patients, and the level of evidence is low. Secondly, the observed outcomes cannot be solely attributed to the corticosteroid therapy due to the combination of multiple drugs. This systematic review is a hypothesis-generating study. Further investigation needs to be done to obtain consecutive samples in a controlled study where the patients are blinded to corticosteroid therapy group and control group. However, the rarity of this event may impede such effort. In that case, the need for reviewing this matter in a systematic way was considered by the authors although good level of evidence were limitedly available.

5. Conclusion

The current systematic review showed that the use of corticosteroid agents is beneficial in improving the outcome of myocarditis associated with COVID-19. The present study showed that no randomized clinical trial has been performed with the aim of assessing the efficacy and safety of using corticosteroids for treating myocarditis associated with COVID-19, thus well-established randomized clinical trials should be pursued in order to confirm the findings of the present review.

6. Declarations

6.1. Authors' Contributions

WK helped in the conception and design of the study. WK, N, CMJ, RBM, AGN, and SD were actively involved in literature search, study selection, data extraction, extensive review, and writing the manuscript. All authors read and approved the final submitted version.

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6.4. Conflict of Interests

The authors report no financial relationships or conflicts of interest regarding the content herein.

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Table 1: Clinical studies that reported the use of corticosteroid in management of myocarditis associated with COVID-19

Authors (Year)	Age	Gender	Complete Assessment	Corticosteroid	Dose	Route	Duration	Other Medication(s)	Outcome(s)
Bernal-Torres et al. (2020) Colombia	38	Female	Fulminant myocarditis associated with COVID-19, cardiogenic shock, and COVID-19 pneumonia	Methylprednisolone	200 mg/day	IV	12 days	Intravenous human immunoglobulin, hydroxychloroquine, azithromycin, lopinavir/ritonavir Norepinephrine, dobutamine, and levosimendan on first day of admission	Clinical improvement, discharged on day-16
Coyle et al. (2020) USA	57	Male	Myocarditis and severe acute respiratory distress syndrome related to COVID-2019	Methylprednisolone	500 mg/day	IV	4 days	Hydroxychloroquine, azithromycin, ceftriaxone, colchicine, tocilizumab, milrinone	Clinical improvement, discharged on day-19
Doyen et al. (2020) France	69	Male	Myocarditis associated with COVID-19, hypertension	Hydrocortisone	N/A	IV	9 days	Aspirin, fondaparinux	Clinical improvement, discharged on day-21
Garau et al. (2020) Belgium	18	Female	Fulminant myocarditis associated with COVID-19, cardiogenic shock, and COVID-19 pneumonia	Methylprednisolone	200 mg/day	IV	8 days	Intravenous human immunoglobulin, hydroxychloroquine, antibiotics Dobutamine and other vasopressors on first day of admission	Clinical improvement, discharged on day-45
Hu et al. (2020) China	37	Male	Fulminant myocarditis associated with COVID-19, cardiogenic shock, and COVID-19 pneumonia	Methylprednisolone	200 mg/day	IV	4 days	Intravenous human immunoglobulin, piperacillin-sulbactam, pantoprazole Norepinephrine, diuretic, Milrinone	Clinical improvement, discharged on day-21
Hussain et al. (2020) USA	51	Male	Fulminant myopericarditis associated with COVID-19, hypertension	Methylprednisolone	N/A	IV	N/A	Dobutamine, indomethacin, azithromycin, hydroxychloroquine, remdesivir, colchicine	Deteriorated after seventh day of admission
Inciardi et al. (2020) Italy	53	Female	Myocarditis associated with COVID-19, heart failure	Methylprednisolone	1 mg/kgBW/day	IV	3 days	Intravenous aspirin, hydroxychloroquine, lopinavir/ritonavir Heart failure treatment: canrenone, furosemide, bisoprolol, and dobutamine in the first 48 hours	Progressive clinical and hemodynamic improvement
Khalid et al. (2020) USA	34	Female	Myopericarditis associated with COVID-19, pericardial effusion, and cardiogenic shock	Methylprednisolone	Not specified (high dose)	IV + Oral	3 days	Colchine, dobutamine, norepinephrine	Clinical improvement, discharged on day-9
Khatri et al. (2020) USA	50	Male	Purulent myopericarditis associated with COVID-19, cardiogenic and distributive shock with multi-organ failure	Methylprednisolone	200 mg/day	IV	2 days	Dobutamine, vasopressin, norepinephrine, hydroxychloroquine, vancomycin, azithromycin, cefepime, and intravenous human immunoglobulin	Death due to multi-organ failure
Li et al. (2020) USA	60	Male	COVID-19-induced myopericarditis, cardiogenic shock, hypertension, hyperlipidemia	Methylprednisolone	200 mg/day (50 mg/6h)	IV	4 days	Intravenous human immunoglobulin, hydroxychloroquine, azithromycin Epinephrine on the first day of admission	Clinical improvement, discharged on day-52
Naneishvili et al. (2020) UK	44	Female	Fulminant myocarditis associated with COVID-19	Methylprednisolone	1000 mg (1st day) 250 mg/day (2 days)	IV	3 days	Milrinone, norepinephrine	Clinically improved, echocardiography result improved
Ortiz et al. (2020) Spain	59	Female	Fulminant myocarditis due to COVID-19, hypertension, cervical degenerative arthropathy, chronic lumbar radiculopathy, lymph node tuberculosis	Methylprednisolone	500 mg/d at tapering dose	IV	14 days	Immunoglobulins, antiviral treatment consisting of IFNB, and ritonavir-lopinavir	Deteriorated with rapid clinical progression to cardiogenic shock. Normal biventricular function was regained within a few days, with severe subsequent dyspnea that required continued ECMO
Richard et al. (2020) USA	28	Female	Fulminant myocarditis associated with COVID-19, diabetes mellitus type 1 with multiple previous episode of diabetic ketoacidosis, diabetic gastroparesis, asthma, anxiety, depression	Methylprednisolone	1 g/day	IV	3 days	Dobutamine, norepinephrine, heparin, insulin, potassium, vancomycin, and piperacillin-tazobactam	Clinically improved on the third day following corticosteroid administration
Salamanca et al. (2020) Spain	44	Male	Fulminant myocarditis associated with COVID-19, cardiogenic shock	Methylprednisolone	1000 mg	IV	1 day	Tocilizumab, hydroxychloroquine, azithromycin, and lopinavir-ritonavir.	Clinical status improved
Sampaio et al. (2020) Brazil	45	Female	Fulminant myopericarditis associated with COVID-19, cardiac tamponade, and refractory circulatory shock	Methylprednisolone	750 mg and 250 mg (1st and 2nd day) followed by 40 mg twice a day)	IV	2 days	Tocilizumab, intravenous human immunoglobulin, convalescent plasma, azithromycin, piperacillin/tazobactam, and teicoplanin Noradrenaline, dobutamine, milrinone and vasopressin.	Clinical improvement, discharged on day-65
Shabbir et al. (2020) UK	50	Female	COVID-19-induced myopericarditis, myositis, hypertension, reactive arthritis	Prednisolone	30 mg	Oral	12 days	Ibuprofen, codeine phosphate, colchicine	Clinical improvement, discharged on day-13
Tavares et al. (2020) USA	61	Male	Fulminant myocarditis associated with COVID-19 and cardiogenic shock	Methylprednisolone	Not specified (high dose)	IV	N/A	Norepinephrine, furosemide, cefepime, doxycycline, hydroxychloroquine, enoxaparin	Death
Zeng et al. (2020) China	63	Male	Fulminant myocarditis associated with COVID-19, severe pneumonia, ARDS, and multiple organ dysfunction syndrome (MODS)	Methylprednisolone	N/A	N/A	N/A	Lopinavir–ritonavir, interferon α-1b, immunoglobulin, piperacillin–tazobactam	The patient died on the 33rd day of hospitalization

Abbreviations: kgBW: kilogram Body Weight; N/A: Not Available; ECMO: Extracorporeal Membrane Oxygenation; IV: intravenous; ARDS: acute respiratory distress syndrome.

Table 2: Assessment of the risk of bias of the included studies

Authors	Were patient's demographic characteristics clearly described?	Was the patient's history clearly described and presented as a timeline?	Was the current clinical condition of the patient on presentation clearly described?	Were diagnostic tests or assessment methods and the results clearly described?	Was the intervention(s) or treatment procedure(s) clearly described?	Was the post-intervention clinical condition clearly described?	Were adverse events (harms) or unanticipated events identified and described?	Does the case report provide takeaway lessons?	Total	Risk of bias
Bernal-Torres et al.	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	87.5%	Low
Coyle et al.	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	87.5%	Low
Doyen et al.	Yes	Yes	Yes	Yes	Unclear	Yes	No	Yes	75%	Low
Garau et al.	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	87.5%	Low
Hu et al.	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	87.5%	Low
Hussain et al.	Yes	No	Yes	Yes	No	Yes	Unclear	Yes	62.5%	Low
Inciardi et al.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%	Low
Khalid et al.	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	87.5%	Low
Khatri et al.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%	Low
Li et al.	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	87.5%	Low
Naneishvili et al.	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	87.5%	Low
Ortiz et al.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%	Low
Richard et al.	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	87.5%	Low
Salamanca et al.	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	87.5%	Low
Sampaio et al.	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	87.5%	Low
Shabbir et al.	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	87.5%	Low
Tavares et al.	Yes	Yes	Yes	Yes	Unclear	Yes	No	Yes	75%	Low
Zeng et al.	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	87.5%	Low

All articles were published in 2020.

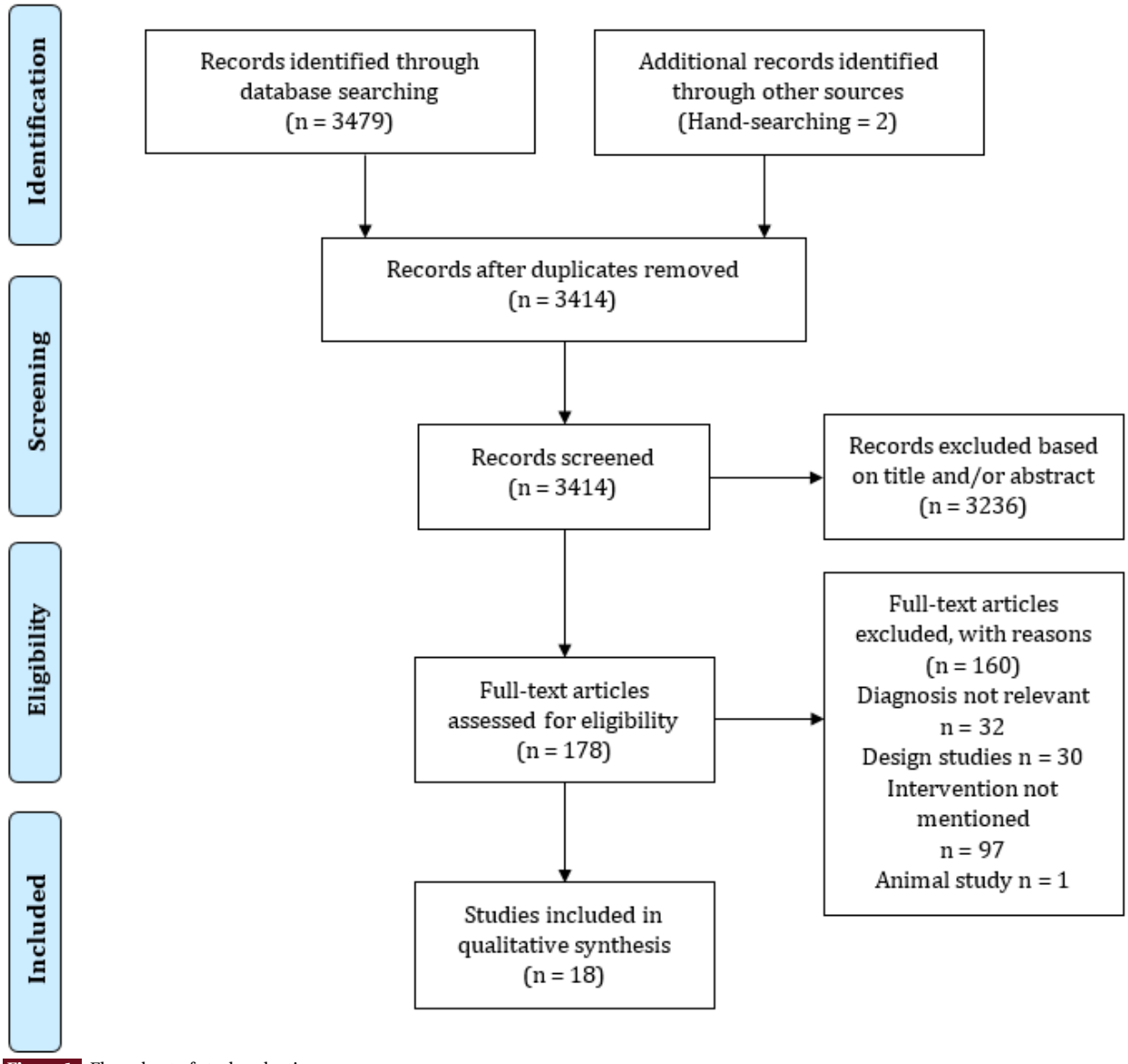

Figure 1: Flow chart of study selection.